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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,550	10/04/2006	Hidetoshi Okabe	20080-00008	1617

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EXAMINER	
NATARAJAN, MEERA	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,550	OKABE, HIDETOSHI	
	Examiner	Art Unit	
	Meera Natarajan	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/17/2006 and 10/16/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-20 will be examined on the merits

Specification

2. The abstract of the disclosure is objected to because of improper use of trademarks. Correction is required. See MPEP § 608.01(b).

The use of the trademark "Herceptin™" has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-20 are directed to non-statutory subject matter. The claims are drawn to an examination method for the administration of an anticancer drug, comprising evaluating usefulness of treatment based on the "examination" of the gene/and or the expressed product thereof the receptor or substance interacting with the receptor. The term "examination" is defined in the specification to broadly encompass mental analytical methods. The specification recites "an examination method for malignant tumors, specifically for therapeutic strategies, predictions of prognosis and anticipations of therapeutic effect in therapy for inhibiting the receptor function of a cell growth factor

receptor by a humanized monoclonal antibody" (p. 1, section [0001]. Thus, the manipulation of data or analysis of data, in this case analyzing expression of a tumor-associated factor receptor and an interacting substance and correlating it with therapeutic effect does not involve any active steps other than mentally comparing results. Consideration of the MPEP at section 2106, Part IV, subpart B, sub-subpart 2, reveals that a practical invention requires the production of a useful, concrete, and tangible result which is reasonably interpreted as at least some physicality of result or representation thereof as required for statutory subject matter. Methods per se as instantly claimed subject matter are reasonably deemed a manipulation of data for such methods, without any physicality, that is, concrete or tangible, requirement. It is noted that the practical invention requirement is directed to a required combination of a useful, concrete, and tangible result which supports this rejection if only one or more of these criteria fail to be met in the claimed subject matter.

4. It is also noted that the broad scope of the claims and definition of "examination" recited in the specification could also include statutory subject matter involving performing an assay to determine the expression of a tumor-associated factor receptor and an interacting substance. The specification discloses on p. 17-18 sections [0033-0035] the term "examination" to include a genetic or immunological method to determine gene or protein expression such as with RT-PCR, southern blotting, immunohistochemical analysis, or detection with an antibody. Therefore, the instantly pending claims can be reasonably interpreted to include two different methods, (1) an examination requiring only mental analytical steps and (2) an examination requiring

active steps to determine gene and/or protein expression. The instantly pending claims under the reasonable interpretation of requiring active step(s) or representation thereof are not rejected hereinunder and will be examined on the merits.

Claim Rejections - 35 USC § 112

5. Claim 1, 2, 3, 5, 6, 8, 9, 11-20 are rejected under 112, first paragraph, because the specification, while being enabling for an examination method conducted for the administration of Herceptin, in order to evaluate usefulness of treatment with Herceptin, comprising in addition to the examination of the gene and/or the expression of HER2/c-erB-2, the examination of the gene and/or expression of MUC4 interacting with Herceptin on the surface of and/or within the cell membrane, does not reasonably provide enablement for an examination method conducted for the administration of any anticancer drug targeting any tumor-associated factor receptor, in order to evaluate usefulness of treatment with said anticancer drug, comprising, in addition to the examination of the gene and/or expression of said receptor, the examination of the gene and or expression of any substance interacting with said receptor on the surface of and/or within the cell membrane. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

6. In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1)

the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

7. The claims are broadly drawn to a method conducted for the administration of any anticancer drug targeting any tumor-associated factor receptor, in order to evaluate usefulness of treatment with said anticancer drug, comprising, in addition to the examination of the gene and/or expression of said receptor, the examination of the gene and or expression of any substance interacting with said receptor on the surface of and/or within the cell membrane.

8. The only working example provided by the specification is the examination of the therapeutic effects with Herceptin can be predicted by examining the combination of HER2/c-erB-2 and MUC4 expression (see Example 1) with patient outcome. No other working examples are provided using other anticancer drugs targeting other tumor-associated factor receptors. Therefore, undue experimentation would be required to support the broad scope of the claims.

9. The unpredictability of determining patient outcome when administered an anticancer drug based on expression of specific genes is well known in the art. Pasche et al. (Best practice research: Clinical Gastroenterology Vol. 16(2) p.331-345, April 2002) teach the unpredictability of correlating molecular markers in prognosis of

colorectal cancer and prediction of response to treatment. Pasche et al. states "the prognostic significance of both *ras* mutations and p21 (known oncogenes) staining has been assessed in a number of reports, with conflicting results. Using polymerase chain reaction to determine K-ras mutations, no association was found between the presence of the mutation, survival or response to therapy" (p. 332-333, last paragraph). In addition Pasche et al. discuss the discrepancies of her-2/neu expression in colorectal cancer patients and its significance to prognosis and that the discrepancies do not currently support its use in the management of patients with colorectal cancer (see p. 333, section "her-2/neu"). With regard to breast cancer, Ross et al. (Seminars in Cancer Biology, Vol. 9(2), p. 125-138; April 1999) review several clinical trials investigating the correlation between HER-2 expression and response to therapy. Ross et al. state "of the studies in which serum HER-2 protein levels predicted response to therapy, three studies found that elevated serum HER-2 neu protein predicted therapy resistance, whereas three studies did not demonstrate this association (see p. 133, right column, lines 10-15). Price-Schiavi et al. (Int. J. Cancer Vol. 99, p.783-791; 2002) teach that a significant number of ErbB2 expressing breast tumors are not responsive to Herceptin (p. 789, right column, 2nd full paragraph). Several groups have investigated the reason for this Herceptin resistance. Price-Schiavi et al. propose another model whereby expression of Muc4 on breast cancer cells that express erbB-2, form a complex with ErbB2 which provides a specific steric block to Herceptin binding. This finding is **NOT** in correlation with the findings of the current application. The current application teaches an examination method wherein treatment with Herceptin of breast

cancer patients that express HER2/c-erbB-2 and Muc4 show a good response (see Example 1). From these teachings, and the lack of working examples to provide evidence for other anticancer drugs targeting other tumor-associated factor receptors, there is insufficient evidence to demonstrate that those in the art would be able to determine therapeutic effects of anticancer drugs by examination of gene and/or product expression.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-20 are rejected under 35 U.S.C. 102(anticipated) as being anticipated by Price-Schiavi et al. (Int. J. Cancer Vol. 99, p.783-791; 2002).

11. The claims are drawn to a method conducted for the administration of Herceptin, in order to evaluate usefulness of treatment with Herceptin, comprising in addition to the examination of the gene and/or the expression of HER2/c-erB-2, the examination of the gene and/or expression of MUC4 interacting with Herceptin on the surface of and/or within the cell membrane. As stated above in the ***35 USC § 101*** rejection, the claimed method can be interpreted two ways, one involving non-statutory mental analytical steps and one involving statutory active steps. The rejection set forth below is directed to the interpretation that the claims read on an "examination" method involving active steps as defined on p. 17-18, section [0033-0035] of the specification.

12. Price-Schiavi et al. teach the expression of Muc4 on MCF-7 breast cancer cells, which express c-erbB-2, form a complex with ErbB2 and provide a steric block to anti-ErbB2 antibody (Herceptin) binding. The reduced binding of antibody would lead to a

reduction in cytostatic effects and sensitization to other chemotherapies (see p. 789, right column, 2nd full paragraph). Therefore, this examination would predict that breast cancer patients that overexpress Muc4 and ErbB2 would not be responsive to Herceptin therapy. Price-Schiavi et al. state "it is now common to screen breast tumors for a variety of molecular markers such as estrogen receptor and ErbB2 to determine the best course of treatment for a breast cancer patient. There is now increasing evidence that Muc4 is aberrantly expressed in a number of different cancers including breast cancers. Thus, along with other tumor markers, it may be useful to screen for Muc4 expression in determining the best course of treatment for a breast cancer patient" (see p. 789-790, right column, last paragraph). As defined in the specification, the "examination" step is drawn to a method involving immunohistochemical analysis of expression of Muc4 and HER2/c-erbB2. The method taught by Price-Schiavi et al. teach immunohistochemistry analysis of solid breast tumor samples obtained from patients with operable breast cancer (see "Material and Methods", p. 784, left column and Figure 1). Therefore, the method taught by Price-Schiavi et al. teach the same active steps of "examination" as the claimed invention.

13. Claim 12 recites "a reagent kit for the use in the examination method according to claim 1". Although the claim recites a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the reference. Therefore, the reference read on the claimed kit. Further, it is a well-known convention in the art to place the recited elements in a kit for the advantages of convenience and economy.

Conclusion

14. Claims 1-20 are rejected

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Meera Natarajan whose telephone number is 571-270-3058. The examiner can normally be reached on Monday-Thursday, 8:30AM-6:00PM, ALT. Friday. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MN

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SUPERVISORY PATENT EXAMINER